Pathologic N0 status in pulmonary adenocarcinoma is predictable by combining serum carcinoembryonic antigen level and computed tomographic findings

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Objectives: It is not clear whether lymphadenectomy has therapeutic benefit in non–small cell lung cancer management. To avoid unnecessary lymphadenectomy, we attempted to identify clinical or radiologic predictors of pathologic N0 disease in patients with peripheral adenocarcinoma.

Methods: From August 1992 through April 1997, 269 consecutive patients with peripheral adenocarcinoma who underwent major lung resection and systematic lymph node dissection were enrolled in this study. We reviewed their contrast-enhancement computed tomographic scans and recorded the maximum dimension of tumors both on pulmonary (pDmax) and on mediastinal (mDmax) window setting images, the largest dimension perpendicular to the maximum axis on both pulmonary (pDperp) and mediastinal (mDperp) window setting images, and the size of all detectable hilar-mediastinal lymph nodes. We defined a new radiologic parameter, tumor shadow disappearance rate (TDR), which is calculated with the following formula:

$$\mathrm{TDR} = 1 - \frac{\mathrm{mDmax} \times \mathrm{mDperp}}{\mathrm{pDmax} \times \mathrm{pDperp}}.$$

Results: In multivariable analysis a lower serum carcinoembryonic antigen level and a higher tumor shadow disappearance rate were significant predictors of pathologic N0 disease. Lymph node size on computed tomographic scanning was not a significant predictor. Among 59 patients with a normal preoperative carcinoembryonic antigen level and a tumor shadow disappearance rate of 0.8 or more, 58 (98%) patients had pathologic N0 disease, and the other patient had pathologic N1 disease.

Conclusions: Mediastinal lymph node involvement was not found in patients with a normal preoperative serum carcinoembryonic antigen level and a tumor shadow disappearance rate 0.8 or more. The patients who meet these criteria may be successfully managed with major lung resection without systematic mediastinal lymphadenectomy.

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Lobectomy or pneumonectomy plus lymphadenectomy (nodal sampling or systematic lymph node dissection) is the standard treatment for patients with resectable non–small cell lung cancer (NSCLC). Lymphadenectomy is essential in staging NSCLC correctly. However, its therapeutic benefit, if any, has not been proven. It is self-evident that lymphadenectomy would have no benefit in

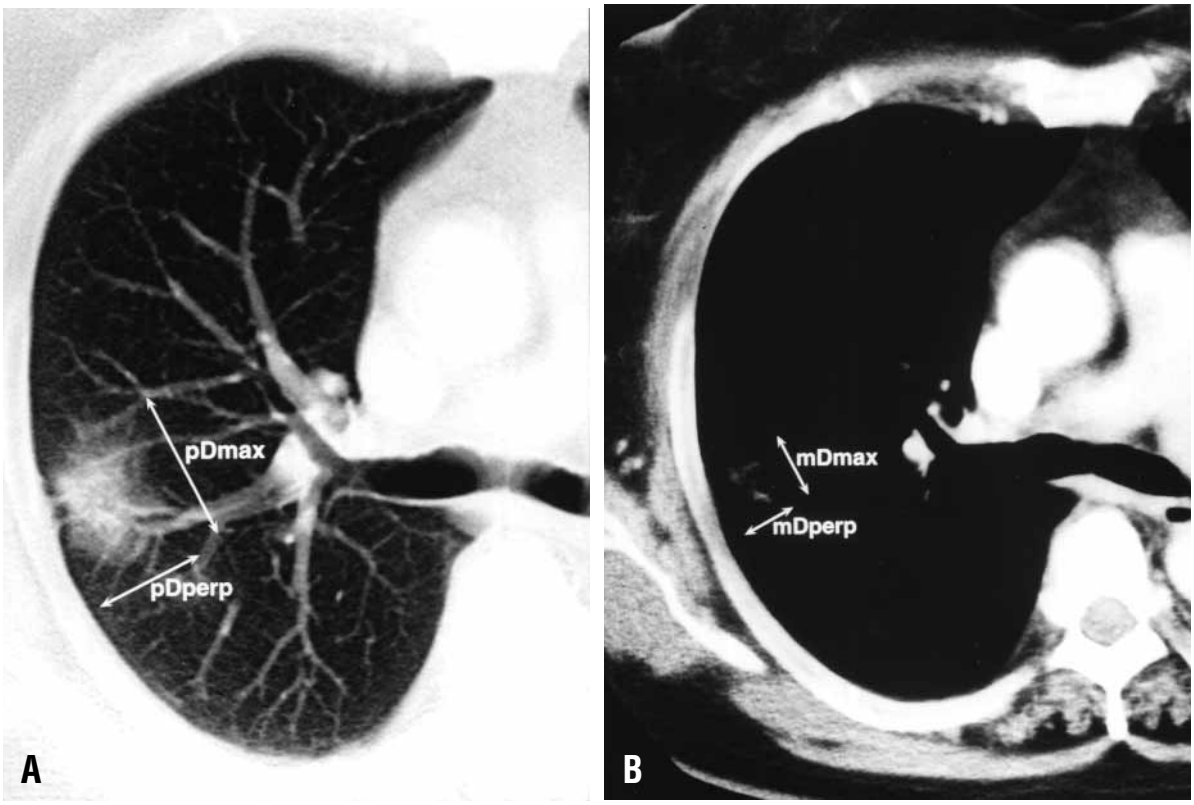

Figure 1. We measured pDmax and pDperp on pulmonary window setting images (A) and mDmax and mDperp on mediastinal window setting images (B).

patients without mediastinal node involvement. If we could correctly predict pathologic N0 (pN0) disease in patients with NSCLC before operation, unnecessary lymphadenectomy could be avoided.

In Japan, many small-sized NSCLCs have been found as a result of the introduction of computed tomographic (CT) screening for lung cancer.[1] However, even NSCLC lesions smaller than 20 mm have considerable potential for lymph node metastasis.[2,3] Small tumor size alone cannot be a reason for omitting lymphadenectomy. Although clinically reliable predictors of pN0 disease would eliminate unnecessary lymphadenectomy, none have yet been established.

In this study we attempted to identify clinical or radiologic predictors of pN0 disease in patients with peripheral adenocarcinoma. We proposed a new radiologic parameter, the tumor shadow disappearance rate (TDR), which was calculated from the tumor shadow sizes on pulmonary window setting images on CT scans and those on mediastinal window setting images.

Materials and Methods

From August 1992 through April 1997, 634 patients with lung cancer underwent surgical intervention at our institute. Among them, all 269 patients with peripheral adenocarcinoma who underwent major lung resection and systematic lymph node dissection were enrolled in this study. Patients who had received induction therapy or had multiple primary tumors were excluded. Contrast-enhanced CT scans were done on an X-Vision/SP system (Toshiba, Tokyo, Japan), and contiguous 10-mm thick sections were obtained from the pulmonary apices to the bases in a supine position at full inspiration. The images were photographed by using a pulmonary window setting (window width, approximately 1500 to 1800 Hounsfield units [HU]; level, approximately –650 to –550 HU) and a mediastinal window setting (window width, approximately 380 to 420 HU; level, approximately 30 to 70 HU). The time interval between CT scanning and surgical intervention was less than a month in all patients.

All CT scans were reviewed by 3 authors (K.T., Y.O., and K.S.), who were not informed of the pathologic outcome, to obtain the following information: the maximum dimension of a tumor on pulmonary window setting images (pDmax); the largest dimension perpendicular to the maximum axis on pulmonary window setting images (pDperp); the maximum dimension of a tumor on mediastinal window setting images (mDmax); the largest dimension perpendicular to the maximum axis on mediastinal window setting images (mDperp); and the size of all detectable hilar-mediastinal lymph nodes.

We defined TDR as calculated by the following formula (Figure 1):

$$\text{TDR} = 1 - \frac{\text{mDmax} \times (\text{mDperp})}{\text{pDmax} \times \text{pDperp}}$$

TABLE 1. Clinicoradiologic characteristics of patients

	Overall	pN0 disease
No. of patients	269	193
Age, y (mean ± SD)	63 ± 10	63 ± 10
Sex, M/F	135/134	99/94
Smoking, pack-years (median [25th-75th percentile])	1.8 (0-37.2)	1.5 (0-34.0)
Pack-years >40	58	36
Pack-years ≤40	211	157
CEA, ng/mL (median [25th-75th percentile])	3.7 (2.3-7.1)	3.1 (2.0-5.6)
Shortest dimension of lymph node, mm (mean ± SD)	6 ± 4	6 ± 4
Longest dimension of lymph node, mm (mean ± SD)	10 ± 6	10 ± 6
pDmax, mm (mean ± SD)	28 ± 12	27 ± 13
pDperp, mm (mean ± SD)	21 ± 9	20 ± 9
mDmax, mm (mean ± SD)	18 ± 14	16 ± 14
mDperp, mm (mean ± SD)	13 ± 11	11 ± 11
TDR (mean ± SD)	0.59 ± 0.30	0.64 ± 0.31

TABLE 2. Relationship between clinicoradiologic factors and pN0 disease: Univariate analysis

Variable	Odds ratio	95% CI	*P* value
Age	1.00	0.98-1.03	.8
Sex (M vs F)	1.17	0.69-1.99	.6
Smoking (pack-years >40 vs ≤40)	0.56	0.31-1.04	.07
CEA*	0.20	0.10-0.38	<.0001
Shortest dimension of lymph node (mm)	0.94	0.88-1.00	.04
Longest dimension of lymph node (mm)	0.96	0.92-1.01	.1
pDmax (mm)	0.98	0.96-1.00	.06
pDperp (mm)	0.95	0.92-0.98	.002
mDmax (mm)	0.97	0.95-0.99	.0006
mDperp (mm)	0.95	0.93-0.98	.0001
TDR	8.38	3.17-22.1	<.0001

CI, Confidence interval.
*Log-transformed serum CEA levels were used.

If multiple nodes within a single station were enlarged, the size of the largest node was recorded. Tumor location was considered to be central when a tumor was located in the inner one third of the lung field on CT scanning and peripheral when in the outer two thirds. Histologic typing was determined according to the World Health Organization classification.[4] The stage of the disease was based on the TNM classification system of the International Union Against Cancer.[5] The mediastinal lymph node mapping on CT scanning and thoracotomy was based on the lymph node map described by Naruke and colleagues.[6] All resected specimens were fixed with formalin and examined microscopically by means of standard hematoxylin and eosin staining. The clinical record of each patient was reviewed for age, sex, smoking status, and preoperative serum carcinoembryonic antigen (CEA) level. Serum CEA was measured by means of the 2-site immunoenzymometric assay (Tosoh, Inc, Yamaguchi, Japan), and the upper normal limit for this assay was 5 ng/mL.

Univariate and multivariable analyses were performed by the logistic regression procedure on StatView 5.0 (Abacus Concepts, Inc, Berkeley, Calif) to determine the relationship between pN0 disease and the following clinical or radiologic findings: age; sex; smoking status (pack-years >40 vs ≤40); serum CEA level; both the shortest and longest dimensions of pulmonary-mediastinal lymph nodes; tumor dimensions (pDmax, pDperp, mDmax, and mDperp); and TDR. The serum CEA level and smoking status (pack-years) were severely skewed. We used continuous variables for age, node and each tumor dimension, TDR, and log-transformed serum CEA levels in statistical analyses. As for smoking status, we used categories (ie, pack-years >40 vs ≤40) because pack-year values showed a 2-peak distribution. TDR was a parameter calculated by pDmax, pDperp, mDmax, and mDperp. Thus, we entered these 5 variables separately in a multivariable model. Differences were considered statistically significant when the *P* values were < .05.

Results

The clinicoradiologic characteristics of the patients are presented in Table 1. There were 193 (72%) patients with pN0 disease among the 269 patients with peripheral adenocarcinoma.

TABLE 3. Relationship between clinicoradiologic factors and pN0 disease: Multivariable analysis

Independent variables*	Odds ratio	95% CI	*P* value
Model 1 (R^2 = 0.16)			
CEA*	0.20	0.10-0.41	<.0001
TDR	6.97	2.33-20.9	.0005
Model 2 (R^2 = 0.12)			
CEA*	0.18	0.09-0.37	<.0001
pDmax	0.99	0.97-1.02	.5
Model 3 (R^2 = 0.14)			
CEA*	0.19	0.10-0.39	<.0001
pDperp	0.96	0.93-1.00	.03
Model 4 (R^2 = 0.14)			
CEA*	0.21	0.10-0.41	<.0001
mDmax	0.97	0.95-1.00	.01
Model 5 (R^2 = 0.14)			
CEA*	0.21	0.10-0.42	<.0001
mDperp	0.95	0.93-0.99	.005

CI, Confidence interval; R^2, determination coefficient.
*Age, sex, smoking status, and the shortest and longest dimensions of pulmonary-mediastinal lymph nodes were also included in the models.
†Log-transformed serum CEA levels were used.

TABLE 4. PPVs of pN0 disease diagnosis in overall patients compared with those in patients with a normal CEA level and those with an elevated CEA level according to various TDR cutoff levels

TDR	Overall (n = 269)	CEA <5.0 ng/mL (n = 167)	CEA ≥5.0 ng/mL (n = 102)
≥0.9	59/64* (92)	46/47 (98)	13/17 (76)
≥0.8	76/81 (94)	58/59 (98)	18/22 (82)
≥0.7	98/113 (87)	75/80 (94)	23/33 (70)
≥0.5	125/156 (80)	94/106 (89)	31/50 (62)
≥0.3	158/218 (72)	115/140 (82)	43/78 (55)

*Number of patients with pN0 disease/number of patients predicted as having pN0 disease on the basis of TDR cutoff level (values in parentheses are given as percentages [PPVs]).

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Univariate analysis revealed 6 potential factors related to pN0 disease (Table 2): TDR; pDperp; mDmax; mDperp; serum CEA level; and the shortest dimension of lymph nodes. The serum CEA level was significant in all multivariable models. Lymph node size on CT scanning was not significant in any model. TDR was a more clinically useful predictor of pN0 disease than pDmax, pDperp, mDmax, or mDperp because both a level of significance on TDR and a determination coefficient were the highest in model 1 (Table 3).

We compared the positive predictive value (PPV) of pN0 disease diagnosis in the overall group of patients with that in patients with a normal CEA level and those with an elevated CEA level according to various TDR cutoff levels (Table 4 and Figure 2). Among 59 patients predicted to have pN0 disease because of a normal preoperative CEA level and a TDR of 0.8 or greater, 58 (98%) patients had true pN0 disease, and the remaining patient pathologic N1 disease.

A comparison between CT size criterion and criteria combining serum CEA level and TDR in diagnosing pN0 disease is presented in Table 5. We used the CT size criterion whereby lymph nodes smaller than 1.0 cm in the shortest dimension were considered not to be metastatic. Specificity and PPV were much higher when criteria combining serum CEA level and TDR were used rather than CT size criterion alone.

Discussion

The accurate preoperative determination of the lack of necessity of systematic mediastinal lymph node dissection in patients with peripheral adenocarcinoma of the lung could have an effect on reducing operation time, degree of invasiveness, and perhaps rapidity of patient recovery. However, no criteria permitting such a determination have yet been established.

The majority of lung adenocarcinomas show a mixture of several subtypes: acinar; papillary; bronchioloalveolar carcinoma (BAC); and solid adenocarcinoma with mucin.[4] They frequently possess a fibrotic focus or scar in the center or beneath the pleura.[7]

BAC is a particular form of lung adenocarcinoma that demonstrates a lepidic growth pattern of tumor cells along the pre-existent alveolar septa. BAC was newly defined as

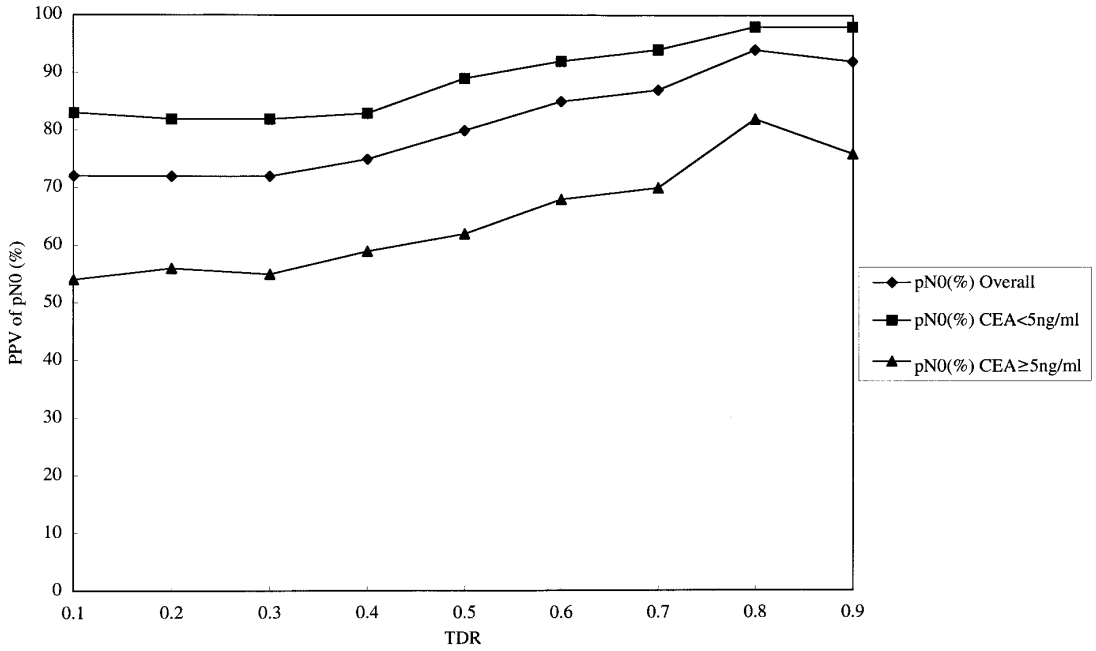

Figure 2. The PPVs of pN0 disease diagnosis in overall patients *(diamonds)* compared with those in patients with a normal CEA level *(squares)* and those with an elevated CEA level *(triangles)* according to various TDR cutoff levels.

an adenocarcinoma without invasive components (ie, stromal, vascular, or pleural invasion) in the latest World Health Organization classification of lung tumor.[4] Noguchi and colleagues[8] reported that the prognosis of adenocarcinomas without a replacement growth pattern (BAC component) is worse than that for adenocarcinomas with a BAC component. The increased prevalence of a BAC component in adenocarcinoma may predict a good prognosis.[9]

Shimosato and associataes[7] first proposed that a central fibrotic focus in lung adenocarcinoma was an important prognostic factor. Suzuki and colleagues[10] showed that the maximum dimension of central fibrosis on pathologic specimens was an independent prognostic factor for peripheral adenocarcinoma of 3 cm or smaller in maximum dimension.

Although fibrotic foci and adenocarcinoma components other than BAC are usually depicted as high-density areas or consolidation on CT scans, the BAC component is reported to be depicted as a hazy increased density area or ground-glass attenuation on high-resolution CT scanning.[11,12] Jang and coworkers[12] demonstrated that ground-glass attenuation on high-resolution CT scanning might represent an early stage of localized BAC.

On the basis of these findings, we speculated that a smaller size of high-density area and a larger size of hazy increased density area on CT scan could be a predictor of less invasive adenocarcinoma. We proposed a new radiologic parameter, TDR, which was calculated from the tumor shadow sizes on pulmonary window setting images and those on mediastinal window setting images. High-density areas in a tumor shadow on pulmonary window setting images would be preserved on mediastinal window setting images, and hazy increased density areas on pulmonary window setting images would disappear on mediastinal window setting images. TDR might represent the ratio of BAC component to invasive component in a tumor. Because a higher TDR would indicate a less invasive lesion, pN0 disease percentage in higher TDR cases would be higher. In

TABLE 5. Comparison between CT size criterion and criterion combining serum CEA level and TDR in diagnosing pN0 disease

	CT size criterion*	Criterion combining CEA and TDR†
No. of predicted patients with pN0 disease	211	59
No. of patients with pN0 disease	154	58
Sensitivity (%)	80	30
Specificity (%)	25	99
Accuracy (%)	64	49
PPV (%)	73	98
NPV (%)	33	36

*N0 disease was defined when all detected lymph node were smaller than 1.0 cm in the shortest dimension.
†N0 disease was predicted when serum CEA level was less than 5.0 ng/mL and TDR was 0.8 or larger.

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this study we confirmed that a higher TDR was indeed a significant predictor of pN0 disease in peripheral adenocarcinoma of the lung.

The other significant predictor of pN0 disease was a normal serum CEA level. We previously reported that in patients with an elevated CEA level, there was a good probability even for normal-sized nodes to be metastatic.[13,14] Although the serum CEA level is known to vary depending on smoking status,[15] serum CEA level did not show multicolinearity with smoking status (Pearson correlation coefficient = 0.23). Furthermore, in multivariable analyses, serum CEA level was proved to be a significant predictor of pN0 disease independent of smoking status.

We showed that cases of pN0 disease can be predicted more correctly by combining preoperative serum CEA level and TDR. Among 59 patients with a normal preoperative CEA level and TDR of 0.8 or greater, all patients but one had pN0 disease. The other patient had pathologic N1 disease. Although this result does not preclude the need for hilar lymphadenectomy, systematic mediastinal lymphadenectomy may be avoided in this population.

Today, video-assisted thoracic surgery (VATS) is applied to a wide variety of thoracic operations.[16,17] One of the important issues concerning VATS lung cancer resection involves the technical difficulties in performing complete mediastinal lymphadenectomy.[2] Patients predicted as having pN0 disease on the basis of serum CEA level and TDR may be good candidates for VATS lung resection.

Specificity and PPV for the diagnosis of pN0 disease were much higher when based on serum CEA level and TDR than when based only on CT size criterion. In deciding not to perform lymphadenectomy, both the specificity and PPV of pN0 disease prediction must be as high as possible because patients who did have hilar-mediastinal node involvement might lose a chance for cure by lymphadenectomy.[18] According to the combined criteria of serum CEA level and TDR, 59 (22%) of 269 patients had correct diagnoses of not having mediastinal node involvement. We could have avoided unnecessary mediastinal lymphadenectomy in about one fifth of all patients with peripheral adenocarcinoma patients.

In conclusion, mediastinal lymph node involvement was not found in patients with a normal preoperative serum CEA level and a TDR of 0.8 or greater. The patients who meet these criteria may be successfully managed by major lung resection without systematic mediastinal lymphadenectomy.

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References

1. Kaneko M, Eguchi K, Ohmatsu H, Kakinuma R, Naruke T, Suemasu K, et al. Peripheral lung cancer: screening and detection with low-dose spiral CT versus radiography. *Radiology.* 1996;201:798-802.
2. Asamura H, Nakayama H, Kondo H, Tsuchiya R, Shimosato Y, Naruke T. Lymph node involvement, recurrence, and prognosis in resected small, peripheral, non-small-cell lung carcinomas: Are these carcinomas candidates for video-assisted lobectomy? *J Thorac Cardiovasc Surg.* 1996;111:1125-34.
3. Takizawa T, Terashima M, Koike T, Watanabe T, Kurita Y, Yokoyama A, et al. Lymph node metastasis in small peripheral adenocarcinoma of the lung. *J Thorac Cardiovasc Surg.* 1998;116:276-80.
4. World Health Organization. Histological typing of lung and pleural tumours. 3rd ed. Berlin: World Health Organization; 1999.
5. Sobin LH, Wittekind C. International Union Against Cancer: TNM classification of malignant tumours. 5th ed. New York: Wiley-Liss; 1997.
6. Naruke T, Suemasu K, Ishikawa S. Lymph node mapping and curability at various levels of metastasis in resected lung cancer. *J Thorac Cardiovasc Surg.* 1978;76:832-9.
7. Shimosato Y, Suzuki A, Hashimoto T, Nishiwaki Y, Kodama T, Yoneyama T, et al. Prognostic implications of fibrotic focus (scar) in small peripheral lung cancers. *Am J Surg Pathol.* 1980;4:365-73.
8. Noguchi M, Morikawa A, Kawasaki M, Matsuno Y, Yamada T, Hirohashi S, et al. Small adenocarcinoma of the lung: histologic characteristics and prognosis. *Cancer.* 1995;75:2844-52.
9. Higashiyama M, Kodama K, Yokouchi H, Takami K, Mano M, Kido S, et al. Prognostic value of bronchiolo-alveolar carcinoma component of small lung adenocarcinoma. *Ann Thorac Surg.* 1999;68:2069-73.
10. Suzuki K, Yokose T, Yoshida J, Nishimura M, Takahashi K, Nagai K, et al. Prognostic significance of the size of central fibrosis in peripheral adenocarcinoma of the lung. *Ann Thorac Surg.* 2000;69:893-7.
11. Kuriyama K, Seto M, Kasugai T, Higashiyama M, Kido S, Sawai Y, et al. Ground-glass opacity on thin-section CT: value in differentiating subtypes of adenocarcinoma of the lung. *AJR Am J Roentgenol.* 1999;173:465-9.
12. Jang HJ, Lee KS, Kwon OJ, Rhee CH, Shim YM, Han J. Bronchioloalveolar carcinoma: focal area of ground-glass attenuation at thin-section CT as an early sign. *Radiology.* 1996;199:485-8.
13. Takamochi K, Nagai K, Suzuki K, Yoshida J, Ohde Y, Nishiwaki Y. Clinical predictors of N2 disease in non-small cell lung cancer. *Chest.* 2000;117:1577-82.
14. Takamochi K, Nagai K, Yoshida J, Suzuki K, Ohde Y, Nishimura M, et al. The role of computed tomographic scanning in diagnosing mediastinal node involvement in non-small cell lung cancer. *J Thorac Cardiovasc Surg.* 2000;119:1135-40.
15. Fukuda I, Yamakado M, Kiyose H. Influence of smoking on serum carcinoembryonic antigen levels in subjects who underwent multiphasic health testing and services. *J Med Syst.* 1998;22:89-93.
16. Wakabayashi A. Expanded applications of diagnostic and therapeutic thoracoscopy. J *Thorac Cardiovasc Surg.* 1991;102:721-3.
17. Landreneau RJ, Mack MJ, Hazelrigg SR, Dowling RD, Acuff TE, Magee MJ, et al. Video-assisted thoracic surgery: basic technical concepts and intercostal approach strategies. *Ann Thorac Surg.* 1992;54:800-7.
18. Izbicki JR, Passlick B, Pantel K, Pichlmeier U, Hosch SB, Karg O, et al. Effectiveness of radical systematic mediastinal lymphadenectomy in patients with resectable non-small cell lung cancer: results of a prospective randomized trial. *Ann Surg.* 1998;227:138-44.